REMARKS

Claims 13-15, 34 have been amended. The claim amendments and new claims find support throughout the application including the drawings and claims as originally filed. No new matter has been added by virtue of the claim amendments.

Applicants gratefully acknowledge withdrawal of rejections and/or objections not reiterated from previous Office Actions.

35 USC §112, second paragraph

Claims 13-14, 34, 15-17, 35-37 stand rejected under 35 U.S.C. 112, second paragraph as being indefinite.

The Examiner rejected the claims for reciting the phrase "represented by SEQ ID NO: 2" in claims 13, 14 and 34. Claims 13, 14 and 34 have been amended in accordance with the Examiner's suggestion. The Examiner also rejected claims 13, and 15 – 17 for reciting the phrase "is at least 70% identical to." Applicants have also amended the claim in accordance with the Examiner's suggestion. In view of the current amendments, Applicants respectfully request withdrawal of the rejection and allowance e of claims 13-14, 34, 15-17, and 35-37.

35 USC §112, first paragraph (enablement)

Claims 13, 15-17, and 32-33 were rejected under 35 U.S.C. 112, first paragraph for lack of enablement. The Examiner considered the claims enabled for a method of identifying a compound useful in the diagnosis or treatment of a human neutral sphingomyelinase related disorder; however, the Examiner considered the invention limited to a recombinant human neutral sphingomyelinase of SEQ ID NO: 2, and not particular fragments of recombinant human neutral sphingomyelinase. Applicants respectfully traverse the rejection.

The instant invention is enabled as claimed. The specification provides examples of suitable neutral sphingomyelinase species for use with the claimed invention that including fragments thereof. The specification provides more than ample guidance towards selecting an appropriate fragment or derivative for use in a particular purpose. For example, the Applicant has provided the deduced amino acid sequence of human neutral sphingomyelinase, including key modification and phosphorylation sites (Figure 2). Applicant has also described

conventional recombinant methods for producing suitable human neutral sphingomyelinase, see for example pages 11-12 of the specification. Further Applicant has defined fragments of human neutral sphingomyelinase and have provided an assay to determine the activity of said fragments through measurement of activity with ^{14}C-sphingomyelin, see for example, pages 8 and 9 and Example 6 of the specification. Human neutral sphingomyelinase fragments with particular amino acid substitutions are disclosed at least at page 9, lines 1-20, for example. Further, Applicant details functional domains of human neutral sphingomyelinase, for example:

> "e.g. TNF-alpha 55nDa receptor/ Fas Apo(o)-1 Domain, the sterol regulatory element binding protein (SREBP) domain, etc.. .TSLKVPA, residues 258-264 of Figure 1; SEQ ID NO: 3....other N-Smase domains can be readily identified by standard techniques such as deletion analysis."

(See specification pages 10-11).

The instant disclosure provides ample description for one skilled in the art to carry out the methods as claimed. See, for example, pages 15-17 of the specification, disclosing particular methods in which suitable enzyme fragments or derivatives are used.

Thus, the specification is enables the claims as written. The specification provides more than ample guidance for selecting an appropriate active fragment or derivative. As such, any testing needed to identify or confirm suitable human neutral sphingomyelinases or fragments thereof for use in the claimed methods is well within the level of experimentation permitted by the Federal Circuit. *In re Wands, 8* USPQ2d 1400 (Fed. *Cir. 1988).* One of skill in the art having read Applicants disclosure would know to identify suitable human neutral sphingomyelinases and fragments t'hereof. Accordingly, for all these reasons, Applicant respectfully requests withdrawal of rejection and allowance of the claims.

35 USC §103 (obviousness)

Claims 13-17 and 32-37 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Chatterjee et al., Ausubel et al., Ogita et al. and Takao et al. or Malmqvist et al.

None of the references, either alone or in combination teach or suggest a **recombinant** human neutral sphingomyelinase or fragment thereof. The arguments regarding the Ausubel and Ogita references are the same as argued in the pervious office action response and as the Examiner has admitted that the previous combination of references do not render the claims obvious, only the primary and the newly cited references are addressed below.

The Chatterjee reference does not teach a **recombinant** human sphingomyelinase, nor give any information or indication regarding said enzyme. The Supplemental Declaration of Dr. Suboroto Chatterjee (dated May 28, 2003) stated that various differences between the natural and recombinant enzymes exist, including that (1) the natural enzyme had tightly associated proteases and phosphatases (2) has an associated (and unwanted) protease activity and (3) the natural enzyme is different from the recombinant version by virtue of being more stable. The Chatterjee reference cited by the Examiner does not suggest any difference between naturally occurring and recombinant human sphingomyelinase, nor does it suggest or provide any motivation to use a recombinant human sphingomyelinase in any method or process. The Examiner alleges that Ausubel et al. provides the requisite guidance to those of skill in the art to manufacture recombinant proteins (12/29/05 Office Action); however with no motivation or reason to make the recombinant enzyme, there is no reason to look to Ausubel et al. for guidance.

Takao et al does not teach or suggest a **recombinant** human neutral sphingomyelinase or fragment thereof. As detailed above, there are clear differences between the natural and recombinant enzyme. In addition, Takao et al teach or suggest "wherein the candidate pharmacological agent modulates the activity of the sphingomyelinase," as the Examiner pointed out on page 12 of the Office Action. Thus, Takao et al. does not cure the defect of the Chatterjee reference.

Malmqvist et al. does not teach or suggest a **recombinant** human neutral sphingomyelinase or fragment thereof. As detailed above, there are clear differences between the natural and recombinant enzyme. In addition, Malmqvist et al. does not teach or suggest "wherein the candidate pharmacological agent modulates the activity of the sphingomyelinase," as the Examiner pointed out on page 12 of the Office Action. Thus, Malmqvist et al. does not cure the defect of the Chatterjee reference.

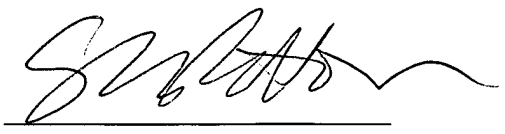
Thus, the claimed invention would not have been prima facie obvious to one of ordinary skill in the art based on the combination of Chatterjee, Ausubel, Ogita, Malmqvist and Takao cited by the Examiner. When considered as a whole, the references provide no desirable suggestion to combine the teachings and render the instant invention obvious. Accordingly, the claims as they currently stand are novel over this combination of references and Applicant respectfully requests withdrawal of the rejection and allowance of the claims.

CONCLUSION

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

Applicatns herewith file a request for a two (2) month extenison of time to extend the date of response to May 29, 2006. Although it is not believed that any further fee is needed to consider this submission, the Office is hereby authorized to charge our deposit account **04-1105** should such fee be deemed necessary.

Respectfully submitted,



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Stephana E. Patton
Reg. No.: 50,373
EDWARDS ANGELL PALMER & DODGE, LLP
P.O. Box 55874
Boston, MA 02205
Telephone: (617) 439-4444
Facsimile: 617-439-4170
Attorneys/Agents For Applicant

Customer No. 21874